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PERNICIOUS MALARIA

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MARIANNA, ARK.

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PERNICIOUS MALARIA.

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CLASSIFICATION AND DISTRIBUTION.

Malaria threatens or destroys life through its inherent dangers, acutely expressed, through the sequellæ of chronic manifestations, or through complications in any stage. Pernicious malaria is that form of malaria, extremely acute, which, *independently of complications*, endangers life in a few hours or a few days. This gravity may be due to the intensification of ordinary malarial symptoms or to the advent of unusual ones. It should be clearly understood that pernicious fever is not a pathological entity but is a form of malaria, from the simple modes of which it sometimes differs only in degree. Its pathogenesis is intimately associated with the life history of the malarial parasite, much more so than is hemoglobinuric fever. Intermediate forms may be encountered which may be difficult to place, as cases with slight somnolence, abundant sweats or cold surface.

Though the pernicious forms of malaria were alluded to by Hippocrates and by Celsus, they did not receive any detailed consideration until 1743, when Torti described them. This pyretologist divided the pernicious fevers into *solitariae*, those characterized by the continuity or acuteness of the ordinary symptoms, and the *comitatae* in which one grave symptom predominated. The *comitatae* he subdivided into the *colliquative*, including the choleraic, dysenteric, artribiliary, cardialgic and

diaphoretic, and the *coagulative*, including the syncopal, algid and lethargic forms.

ALIBERT¹ in 1804 distinguished twenty varieties of pernicious malaria.

ROUX², following Jaccoud's classification, looks on all as originating in the vaso-motor and sympathetic systems, or in the cerebro-spinal system.

KELSCH and KIENER³ adopt Torti's system with slight modifications.

MARCHIAFAVA and BIGNAMI⁴ arrange the pernicious forms, according to the course of the temperature, into tertian, quotidian, sub-continuous and larval.

MANSON⁵ groups them roughly into cerebral—including the hyperpyrexial, comatose, convulsive and paretic forms—and algid, including the syncopal, choleric, dysenteric and hemoglobinuric forms.

DANTEC⁶ classifies the varieties anatomically according to the organs which bear the brunt of the attack, namely: (1) The brain, (2) the medulla, (3) the spinal cord, (4) the heart, (5) the lungs, and (6) the digestive tube.

HOMEM⁷ describes fifteen definite forms, besides several undefined varieties. CARDAMATIS⁸ distinguishes seventeen varieties.

More than thirty so-called varieties of pernicious malaria have been described. A partial list of these includes the apoplectic, ataxic, comatose, sudoral or diaphoretic, delirious, eclamptic or convulsive, tetanic, typhoid, amaurotic, aphasic, ardent, exanthematous, hemiplegic, hydrophobic, neuralgic, cerebro-meningeal, cardialgic, dyspnoeic or asthmatic, pneumonic, pleuritic, syncopal, hemoptoic, algid, choleraic, dysenteric, gastric or gastralgic, hemorrhagic, bilious or hepatic, lymphatic, rheumatic and nephritic forms.

This multiplicity is due to two causes, first, the fanciful and unnecessary subdivision of typical forms; secondly, the mistaking of complications for true pernicious attacks.

Any classification is not absolutely essential, and all are more or less arbitrary. Nevertheless, for convenience, all forms of true pernicious malaria may be easily and logically arranged into (1) cerebro-spinal, (2) thoracic, and (3) abdominal forms.

Pernicious malaria is fortunately becoming rarer in the United States, and is now only occasionally seen except in the South. The affection presents itself especially in Texas, Arkansas, Louisiana, Mississippi, Alabama, Georgia, Florida, the Carolinas and Virginia, and autochthonous cases are met with at least as far up the Atlantic coast as New York. It is more prevalent along the valleys of the large rivers, and occurs at least as far north as Missouri and Illinois. In the Pacific slope it is rare, but is occasionally encountered in the river valleys of California. In Mexico it is found in the region of both coasts, and is common in Central America. In South America it is frequent along the northern coasts of Colombia and Venezuela. Guiana is the malarial focus of South America. Not a few cases are seen in Northern and Eastern Brazil and along the valleys of the Amazon and its tributaries. On the west coast cases occur probably as far south as Peru. In most of the Greater and Lesser Antilles pernicious malaria is endemic.

In some of the low-lying portions of Holland and Belgium cases are now but rarely seen. In France it is the southern and western portions, especially the valley of the Loire, at least as far up as Saumur, in which this form of the disease is now and then found. Occasional cases occur in the valleys of Spain and Portugal. All the European coast lands bordering on the Mediterranean, Adriatic and Aegean seas, especially Greece and Italy and the islands of Sicily and Sardinia, present numerous cases, and it is not infrequent along the coasts of the Black and Caspian seas. In Italy it is chiefly the southern and west central portions that are most severely scourged.

Pernicious malaria is sometimes seen in Asia Minor, parts of the coast of Arabia, and on the Island of Cyprus. In Central Asia, Turkestan affords a few cases, especially in the vicinities of Samarkand and Merv. In India, cases are seen in most of the coast regions and in Punjab, Assam and the Terai. It is known on the Island of Ceylon, especially near the coast. Parts of Burmah, Siam, the Malay Peninsula, Tonquin and Cochin China are hotbeds. Cases are observed in Southern China, rarely as far north as Pekin. The East Indies are highly notorious, and recently cases are being reported from the Philippines. Formosa is a home of the disease.

Portions of Africa are the most intense foci of pernicious malaria of the world. On the west coast it prevails from Angola to Senegal, and on the east from Portuguese East Africa to Eritrea. On the north it is sometimes seen in portions of Algeria and the lower valley of the Nile. In the interior it is especially frequent in the valleys of the great rivers and lakes. It is very fatal in Madagascar, Reunion, Mauritius and certain of the Comoro Islands.

It is impossible to arrive at any definite knowledge of the proportion of malarial cases that are pernicious, since writers vary in their conceptions of what constitutes perniciousness. However, the following list of cases will give a fairly correct idea. In the first column is recorded the locality, in the second the reporter, in the third the number of cases of malaria, and in the fourth the number of these cases that were pernicious:

Java	Van der Scheer ⁹	105	6
St. Lucia	Gray and Low ¹⁰	137	8
Algeria	Billett ¹¹	400	40
Greece	Kanellis and Cardamatis ¹²	60125	127
Tropics Generally	Kanellis and Cardamatis ¹²	277000	3054
Philippines	Chamberlain ¹³	120	1
Trinidad and Tobago	De Wolf ¹⁴	12051	119
Guiana	Maurel ¹⁵	8516	281
Veneto	Bianchi ¹⁶	203	1
Saumur	Laveran ¹⁷	118	1
Guatemala	Laveran ¹⁷	2345	118
Madagascar	Burot and Legrand ¹⁸	2036	25
Selangor	Travers ¹⁹	3392	260
Greece	Cardamatis ²⁰	2506	50
Mortara	Pezza ²¹	1121	60
New Orleans	Hospital Reports ²²	778	8
Baltimore	Thayer and Hewetson ²³	616	3
Madagascar	Laveran ¹⁷	1750	11
Total		373319	4173

This gives a general average of about one case of pernicious to ninety of malaria.

The list below shows the proportion of deaths from pernicious malaria to deaths from all varieties of malaria, the first column of figures showing the number of deaths from all types of malaria, the second the number of deaths from pernicious malaria:

Holland	Schoo ²⁴	2017	727
French Tropics	Burot and Legrand ¹⁸	1401	325
Soudan	Burot and Legrand ¹⁸	307	93
Tonking	Burot and Legrand ¹⁸	405	126
Tonking	Rey ²⁵	192	79
Total		4322	1350

These figures would lead us to infer that about thirty-one per cent. of deaths from malaria are due to pernicious malaria.

In the region of the Valtellina, in eight years GALLI-VALERIO²⁴ saw only two cases of pernicious malaria. BORIUS²⁶, in Senegal, saw 600 cases from 1863 to 1872. HOMEM⁷ had 68 cases in the years 1866-1875 at Rio de Janeiro. JACOBS²⁷ saw in Cuba in eight years four cases. In Rome 4 per cent. of estivo-autumnal infections are said to be comatose attacks, and in Cochin China²⁸, 16 per cent. In Constantine LAVERAN¹⁷ found one pernicious attack to 35-40 malarial cases, and states that in Senegal the proportion is 4.1 per cent. According to this authority, in French Congo in 1897, of 23 deaths from all causes, four were due to pernicious malaria.

Generally speaking, the comatose variety is by far the most common, and the algid type second in frequency. There are, however, a few exceptions. In regions of South America, as parts of Guiana¹⁵ and in Rio de Janeiro⁷, the algid seems to be the most frequent. In Cochin China⁶ the choleraic form is said to predominate, but some of the cases may be true cholera. In 1466 pernicious cases collected by KANELIS and CARDAMATIS¹² there were only 8 of dysenteric pernicious. BILLET¹¹ found the typhoid form relatively frequent in Algeria, reporting forty cases, which constituted 10 per cent. of the cases of malaria in his experience.

Fifteen hundred and fifty-nine cases, collected by the writer from various sources, may be distributed as follows:

Cerebro-spinal forms	1256
Thoracic	16
Abdominal	287
	1559

Both the frequency and mortality vary, sometimes greatly, from year to year. At times its occurrence has been so severe as to attain the significance of an epidemic. Mannaberg mentions an epidemic of comatose malaria which occurred in 1730.

HERTZ³⁰ states that it may prevail in epidemic form, and describes an epidemic that took place on the west coast of Nicaragua in May, 1868, but from his description of the symptoms these cases may have been yellow fever. In depicting the great epidemic of 1866-67 in Mauritius, DAVIDSON³¹ says that comatose and algid seizures were numerous. DAVIDSON alludes to several other epidemics. In the Haiderabad epidemic of 1843 the onset was frequently with vomiting and purging of blood and epistaxis. The fatal issue was usually with coma. In the Gazeepur epidemic of 1859 the patients became comatose, or semi-comatose, after a day or two. In the valley of the Ganges in 1869 an epidemic of algid fever occurred, which was highly fatal. In the Burdwan epidemic the comatose form predominated. Probably the most fatal epidemic on record is that of Edam Island at the beginning of the last century, where every one of the seventy-six marines who landed were attacked with pernicious fever and at least sixty-six died. CARDAMATIS³² states that epidemics of comatose malaria occurred in Rio de Janeiro in 1556, 1784, 1808, 1829, 1832 and 1837, and that such epidemics have also occurred in Greece. After the construction of Port Swettenham, British Malaya, in 1901, a severe outbreak of malaria occurred, and there were 52 deaths in the district hospital.

ETIOLOGY.

In America pernicious malaria is rarely seen in the adult negro, by far the greater number of cases occurring in this race being in children under ten. This coincides with the experience of those who have practiced among the blacks of Africa. It is not common among the natives of Algeria or Arabia. The natives of India are not immune and the Chinese are very susceptible. KOCH³³ relates that of 273 Chinese imported from Hong Kong to Stephansort in 1898, 125 died within the course of a year, mostly of malaria.

More cases occur in males than in females. This is not because of greater susceptibility, but on account of more frequent exposure of the male sex. CRESPIN³⁴ believes that pregnancy may render pernicious, attacks that have no grave tendencies. He accounts for this through hepatic insufficiency. BELL³⁵ reports a case of comatose malaria in a Chinese woman who was eight months pregnant. Premature delivery occurred on the second

day, the child being dead, and the mother died on the seventh day. DOS SANTOS³⁶ describes a case of algid malaria in a woman, age 27, six months pregnant. Abortion occurred thirty-six hours after onset of the attack. The placenta was enormous. The woman recovered. Ten months later the same woman was assailed with a similar attack while six months pregnant. She aborted again and made a good recovery.

Children are prone to pernicious attacks, especially of the cerebral type. Sixty-nine cases observed by MARTIRANO²⁴ give the following age distribution:

Under 9 months	6
One year old	19
Two years old	12
From 3 to 4 years	8
From 5 to 10 years	5
From 10 to 30 years	5
From 30 to 70 years	14
	69

In another series of 25 under MARTIRANO'S²⁴ care, 13 were children and 12 were adults. In 31 cases of TANZARELLA²¹ 19 were under 10 years of age and 12 older. CACCINI'S²⁴ 99 cases show an unusually small per cent. in children, only 14 cases occurring in children under 10 years of age.

The convulsive form is relatively frequent in children living in highly malarial countries. According to THORNHILL³⁷ in Ceylon during 1896, 40.52 per cent. of children dying under one year of age died of convulsions, most of which were due to malaria. Speaking of pernicious malaria in British Malaya, TRAVERS¹⁹ says: "The infant mortality on some estates, where the coolies suffer much from fever, is terribly high. I know of one estate (since abandoned) on which a large Tamil labor force was employed where *all* the infants died. The manager offered a reward for the first child successfully reared on the estate, but that reward was, I believe, never claimed."

Convulsive pernicious is apt to attack children with nervous predisposition, either hereditary or acquired. It is rare in adults, though MAUREL, REYNAUD and DUBERGE have seen such cases.¹⁷ The aged are more susceptible to comatose attacks.

In the Southern States pernicious malaria is more prevalent at the height of the malarial seasons, especially in July, August

and September. In Southern Europe and in Algiers the season is said to be from July to November. In Greece cases appear in July, are most frequent in autumn, and are rare in winter. In India it is at the acme of the malarial season that these attacks occur.

Eleven hundred and one cases from various sources are distributed as follows:

	Candé, ²⁵ Cochin China.	Martirano, ¹⁶ Italy.	Tanzarella, ²¹ Italy.	Billett, ¹¹ Algeria.	Caccini, ²⁴ Italy.	Martirano, ²⁴ Italy (1901)	Total.
January	39		1				40
February	43						43
March	80						80
April	99		1				100
May	110		1	1			112
June	126		2	1	1		130
July	115	1	8	2	4	5	135
August	79	5	10	11	18	25	148
September	54	10	3	13	7	21	108
October	52	5	2	12	12	7	90
November	47	4	3		12	6	72
December	36				2	5	43
Total	880	25	31	40	56	69	1101

The influence of inundations on the etiology of pernicious fever is well recognized. In 1826 JOHNSON³⁸ wrote: "There is no unmixed good in this world. The inundations of the Nile and the Ganges, while they scatter fertility over the valley of Egypt and the plains of Bengal, sow with a liberal hand at the same time the seeds of dreadful diseases." This is in all probability true of the Mississippi and other large rivers of our country. In 1854 FRERICHS recorded an epidemic of pernicious malaria following an overflow of the Oder, where there had previously been only mild cases of malaria.

The length of residence in a malarial region is probably not an important factor in the etiology of the affection. While SIMS³⁹ and others believe that it occurs mainly in the early period of residence, most of MAUREL'S¹⁵ cases were in persons who had been in the colony a long time. PLEHN⁴⁰ mentions the case of a young physician who died of pernicious malaria six days after arrival at Banana.

MAUREL¹⁵ states that outbreaks of pernicious malaria may occur several years after return to France from the tropics, and without new infection. During and shortly after the war with Spain numerous cases which were infected in Cuba and the Philippines were treated in American hospitals. REES⁴¹ records the case of a man who had spent only five days in an endemic region and developed comatose malaria with fatal termination in a few weeks after his return to London. SATTERLEE,⁴² HALL,⁴³ NEER⁴⁴ and others have observed similar cases in America. In the majority of such cases the outbreak occurs within a few weeks after leaving the endemic area.

Occupations which subject not only to malarial infection but to hardships and exposure, especially to the sun, predispose to pernicious attacks. MANSON⁵ cites the case of Hong Kong, formerly healthy enough, but when barracks and houses were being built and roads laid out, the soldiers died by the hundred of pernicious fevers. HOMER⁷ asserts that these cases occur in Rio de Janeiro, particularly when the sewerage, gas and water companies are making deep and extensive excavations in the more central streets of the city. Early in the last century, when the marsh of Chartreuse, near Bordeaux, was drained, an epidemic of severe malaria prevailed, and in 1805 twelve thousand people were stricken, of whom three thousand died in five months.

As it is especially in the laboring and poorer classes that primary infections often do not receive adequate treatment, it is largely in this class that pernicious attacks are found.

Pernicious attacks may be first attacks, or they may occur in cachectics, but it is chiefly between these extremes that most attacks originate, namely, in those having had previous attacks of malaria, but who are not saturated to the degree of cachexia. LAVERAN¹⁷, MARCHIAFAVA and BIGNAMI⁴, and SAMBON⁴⁵ have never seen pernicious attacks without previous malaria. RUGE²⁸ however, states that such cases are not uncommon in India and both the east and west coasts of Africa. COLIN and ANTONIADES have observed like cases.⁴⁶ WURTZ and THIROUX⁴⁷ say that the typhoid form is most often a fever of first invasion. ROUX² knows of numerous examples of pernicious fever as the first manifestation of malaria. MANNABERG²⁹ asserts that it may attack those who have never before suffered from malaria, as well as

those who have undergone repeated attacks. HOMEM⁷ says that in many cases the pernicious paroxysm is preceded by simple ones; in others the patient is attacked while in perfect health. It is the comatose form that is most frequently seen in those who have not previously been attacked with malaria. CRESPI³⁴ experience is that the attacks are exceptional in chronic malarials. SMART⁴⁸ records it that during the civil war pernicious attacks occurred not only in persons who were for the first time exposed to a highly malarial atmosphere, but also among those who had suffered more or less from the malarial influence before the super-vention of the congestive seizure. In fifty cases observed by CARDAMATIS and DIAMESSIS,⁴⁹ only one developed as a primary attack. Most of the algid and comatose cases of MAUREL¹⁵ were in subjects of chronic malaria. THAYER⁵⁰ and CRAIG⁵¹ say that it is customary for malarial paroxysms to precede. SCHELLONG⁵² agrees with Martin that pernicious fever attacks persons already rendered anaemic from malaria.

While it is probably true that in the majority of instances typical paroxysms precede pernicious attacks, it is of the utmost importance to bear in mind that the latter may be manifestations of first invasion. "If there are cases of pernicious fever, in which the patient has been attacked previously by paroxysms of simple, well-marked or masked intermittent, there are also cases, unhappily numerous, in which it is the pernicious attack that opens the scene, where the subject, in the enjoyment of the most flourishing health, is treacherously assailed by the terrible enemy without the least signal to warn of the enormous peril awaiting him." (HOMEM.)

Pernicious malaria is almost as varied in pathogenesis as it is in its manifestations. Not only are its several forms associated with unlike conditions, but for the explanation of some the presence of several different factors is necessary. Thus, comatose malaria may be associated with at least two different forms of the parasite; the peripheral blood may show very great numbers of these parasites, or they may be scanty; in the brain they may be found in hordes, even to the occlusion of small vessels, or they may be entirely absent.

As may be inferred, no one etiological element can account for all cases, even of the same type. Probably the only essentially common factor is the presence of the malarial parasite, the mani-

festations of which run the gamut from the mildest intermittent to the profoundest cachexia, from the most artfully masked to the deadliest pernicious.

Until comparatively recently it was believed that infections with the so-called benign organisms never gave rise to pernicious symptoms. CELLI⁵⁴ states that the tertian and quartan parasites never cause pernicious fevers. MARCHIAFAVA and BIGNAMI⁵⁵ say that there is no instance on record of a malignant fever following tertian and quartan infections, and that no autopsy has ever been made in connection with a malignant spring tertian or quartan. MANNABERG,²⁹ VAN DER SCHEER⁹ and MAURER⁵⁶ believe that only the estivo-autumnal parasites have a rôle in the production of the pernicious fevers. THAYER, in his "Lectures on the Malarial Fevers," says that he never heard of a pernicious paroxysm occurring in tertian or quartan infections, with the exception of the case of FRENCH.⁵⁷

While the vast majority of cases of pernicious malaria are due to the infection with the tropical parasites, it cannot now be maintained that tertian and quartan infections are not occasionally accompanied by perniciousness. CRAIG⁵⁸ says that any of the malarial parasites may cause pernicious infections, leading to death. CRESPIN⁵⁹ informs us that it is not rare to find on examination tertian and quartan parasites in these cases. BILLETT¹¹ found the large tertian in six of forty cases of typhoid pernicious. ZIEMANN²⁶ observed a case of pernicious malaria due to the benign tertian. THIROUX¹ found this parasite in a case of convulsive pernicious in a mulatto infant. EWING,⁶⁰ in sixty-four cases of the cerebral type of pernicious, found the large tertian parasite alone in five. FRENCH⁵⁷ reports a case of comatose malaria in a man, aged 21, whose blood harbored the tertian parasite. HUNT⁶¹ observed a case of common tertian complicated by alarming hematemesis in a boy aged 11. McELROY⁶² had a case of comatose pernicious due to tertian infection in a negro male, aged 30. FICUCCI⁶³ records a case with a pernicious meningo-cerebellar syndrome, due to tertian parasites. FENNER⁶⁴ gives the history of a case of the comatose type in an adult; the blood examinations showed crescents and large tertian forms.

CRAIG⁵⁸ makes the assertion that quartan infections are more apt to become pernicious than tertian. The writer, however,

agrees with DAVIDSON³¹, who says that pernicious symptoms occur more rarely in connection with the quartan infections than with simple tertian. The reasons for this are probably the relative rarity of quartan fever and the more even distribution of parasites throughout the circulation, there being slight tendency to form accumulations.

It is not yet known with certainty which variety of the estivo-autumnal parasite gives rise most frequently to perniciousness. MARCHIAFAVA and BIGNAMI⁵⁵ and MANNABERG²⁹ hold that the tertian estivo-autumnal infections are the most dangerous, only a few cases showing the quotidian. CRAIG⁵¹, however, found the quotidian parasite most often in cases infected in Cuba and in the Philippines. This was also the experience of WRIGHT⁶⁵ in British Malaya, who found the pigmented quotidian parasite most frequently associated with the cerebral and gastro-intestinal types of pernicious malaria.

The part played by the crescents in the pathogenesis of pernicious paroxysms is worthy of brief consideration. MARCHIAFAVA and BIGNAMI,⁴ CELLI,⁵⁴ MANNABERG,²⁹ A. PLEHN,⁶⁶ KOCH,⁶⁷ MANSON,⁵ THAYER⁵⁰ and others, believe that this form of the organism is non-pyrogenic. EWING,⁶⁸ however, holds with LAVERAN, that it is by no means certain that the formation and development of the crescents are entirely innocuous to the patient. EWING, doubtless in part, bases this opinion on the finding of crescents alone in thirty-three of sixty-four cases of cerebral pernicious.⁶⁰ Whether the blood examined in these cases was peripheral or visceral is not stated, but as only three were fatal it may fairly be assumed that in most instances at least it was peripheral. That the crescentic form of the parasite has an intimate relation to the production of the pernicious fevers is improbable, for the following reasons: First, crescents alone may be found in the peripheral blood, and intense localization of active forms be present in the brain or other viscera. The number of parasites in the superficial circulation is not a reliable guide to the severity of the attack. Of Ewing's sixty-four cerebral cases no parasites were identified in eleven, and in many of his thirty-three cases in which crescents alone were found, the search was successful only after one and two hours. Secondly, crescents are rarely, if ever, present in the parasitic localizations and thrombi frequently observed in pernicious cases.

Of the pathogenetic factors which excite perniciousness, the following are to be regarded as the most important and approximately of relatively equal importance:

1. An excessive number of parasites.
2. Localizations of parasites.
3. Toxins.
4. Individual predisposition and external etiologic influences.

NUMBER OF PARASITES. GOLGI'S law, that the number of parasites determines the severity of the attack, has been generally accepted. Cases in which the parasites are in very great numbers in the peripheral blood are usually accompanied by coma.

We have no means of estimating even approximately the total number of malarial parasites in the body of a malarial patient, as the distribution of the former varies within the widest limits. They may be numerous in the peripheral and visceral circulation generally; they may be scanty or absent in the peripheral circulation and numerous in the most of the viscera; or they may exist in moderate numbers or be absent except in certain areas where they may be intensively localized. That the parasites are abundant, either absolutely in the body as a whole, or relatively in certain areas, probably holds good in a great majority of the cases, though, as CELLI⁵⁴ states, we cannot always attribute perniciousness to the large number of parasitic forms. MARCHIAFAVA and BIGNAMI⁴ call attention to certain grave cases of comatose, convulsive, delirious or mixed pernicious, in which from beginning to end and even at autopsy very few parasites are found. MANNABERG²⁹ says: "From the general impression which I have obtained, naturally from the peripheral blood, the number in malignant fevers is perhaps larger, yet the difference scarcely seems so decided as to make this factor alone responsible for the perniciousness."

As applied to the number of parasites in the peripheral blood, GOLGI'S rule is applicable only in a very general sense. ZIE-MANN⁶⁹ states that the number of parasites in the peripheral blood is not always in direct relation to the severity of the attack. CRESPI³⁴ acknowledges that he had difficulty in finding the parasites, which were always scanty in these cases. He gives the details of a case in which there were neither parasites nor pigment in the peripheral blood, but they were numerous in the vessels of certain viscera. This writer quotes NOCHT as say-

ing: "In pernicious attacks the hematozoa are not found in the peripheral blood, but only in the viscera." MOORE⁷⁰ says: "I have often seen cases where the symptoms in no wise seemed commensurate with the number of parasites observed in the specimen of blood." According to KENDALL⁷¹ there may be only a few parasites in the peripheral circulation, or it may be even impossible to find them. MANNABERG²⁹ states that it sometimes happens that the peripheral blood is very poor in parasites. MARCHIAFAVA and BIGNAMI⁴ note the fact that the contradiction found so often during life between the number of the parasites and the gravity of the disease disappears when an autopsy allows of an examination of all the organs. CRAIG⁵¹ asserts that "the number of parasites found in the peripheral blood is not always a criterion as to the perniciousness, as one of the most rapidly fatal cases I have ever observed showed but few parasites in the peripheral blood." To quote BARKER⁷²: "In the estivo-autumnal infections the number of organisms circulating in the peripheral parts affords, as a rule, very insufficient data upon which to base an idea of the severity of the infection." THAYER⁵⁰ says that there may be very few parasites in the peripheral circulation. He mentions a fatal case of the comatose variety showing no active parasites in the peripheral blood, and only a few ovoids and crescents after a careful search of the blood, obtained by puncture of the spleen. MARCHOUX⁷³ reported three cases of pernicious malaria, in which the parasites were very scanty in the peripheral circulation. ZERI⁷⁴ records four cases of pernicious fever, in all of which the parasites were few in number. BLOOMBERGH and COFFIN⁷⁵ treated a case ending fatally in which no parasites could be found until forty-eight hours after onset, notwithstanding repeated examinations. In seven cases in which FENNER⁶⁴ examined the blood, no parasites were found in five. EWING'S⁶⁰ eleven cases of the comatose form, in which no parasites were fully identified, have been mentioned. I have observed one case of severe comatose malaria in a boy aged 12, in whose peripheral blood the parasites were scanty.

On the other hand, the superficial circulation may be teeming with parasites, while the patient experiences only a mild attack. Thus A. PLEHN⁷⁶ gives the history of two cases in which the symptoms were slight, though the peripheral blood showed as

many as thirty-five and forty-six tropical parasites, respectively, to each field of the microscope.

It is highly probable that an enormous number of parasites, equally distributed, depends for its power to elicit pernicious symptoms upon the increased quantity of toxin elaborated.

LOCALIZATIONS OF PARASITES. Accumulations of parasites in the brain were first described by PLANER (1854), and by FRIEDRICH (1861); those in the liver by GUARNIERI (1867). More recently the minute observations of MARCHIAFAVA and BIGNAMI, DOCK, BARKER and EWING, have taught us that pernicious malaria, in many of its varied manifestations, is dependent on these localizations in one or more of a multiplicity of localities. Localizations in the brain have been found associated with a wide variety of cerebral symptoms; in the mucosa of the alimentary tract, with gastro-intestinal symptoms and typical algid attacks; in the heart, with cardiac symptoms; in the medulla, with bulbar paralysis; in the retina, with amblyopia; in the pancreas, with hemorrhagic pancreatitis, etc. In proportion to the amount of damage sustained by the kidneys in malaria there is less tendency for parasites in pernicious attacks to accumulate in these organs than in any other of the body. The most carefully studied case of this condition is that of EWING.⁷⁷

These localizations consist, in the main, of parasite-infected red blood cells. There may be, however, pigmented leucocytes and free parasites and pigment. The parasites in each particular case may be of the same or of different stages of development. The pigmented and sporulating forms are probably oftenest seen, but the earlier phases are frequently observed. It would seem reasonable that the crescents, on account of their size, would frequently form an important element in these accumulations of parasites, but such does not appear to be the case.

The cause of the parasitic concentrations is problematical. It cannot be due to the size, weight or loss of elasticity of the infected cells, for as MANNABERG²⁹ states, the benign parasites would be more apt to form thrombi if this were the cause. KELSCH and KIENER³ and others have observed endothelial swellings in the small cerebral vessels, with consequent constriction of calibre, but whether this is a cause or an effect cannot be said. Vaso-motor disturbances and phagocytosis have also been invoked in explanation. The most probable theory is that of MANNA-

BERG²⁹, who attributes the condition to a sort of agglutination or adhesiveness that holds the erythrocytes to the vessel walls.

The symptoms present in cases in which, on post-mortem examination, localizations of parasites are demonstrated, are not always referable to these aggregations alone, since changes are frequently observed which are secondary to parasitic thrombosis, and may outweigh the latter in pathogenic importance.

The most conspicuous of these changes are perivascular exudation, hemorrhage and necrosis. The hemorrhages are usually punctate, but BLANC⁷⁸ and ZIEMANN⁶⁹ report large cerebral clots.

This propensity of the parasites in pernicious fever to congregate undoubtedly explains the course of many cases, but by no means all. Fatal cases of comatose malaria have been observed with no parasites at all in the brain. FORD⁷⁹ reports a case with serious pulmonary symptoms, in which the parasites were no more numerous in the lung than in the general circulation. "The severity of the renal lesion, with the absence of parasites in the renal vessels, also requires mention."⁸⁰

It is not known whether parasitic thrombi may exist without producing symptoms. FRERICHs,²⁶ who frequently observed thrombotic occlusions of the cerebral vessels, insisted that too much stress should not be laid on them, on account of the rich collateral circulation. He likewise affirmed that he had more than once seen markedly pigmented brains without cerebral symptoms during life.

Based on a case in which the patient was suddenly attacked with transient coma three times in five days, EWING⁸⁰ believes that embolic processes are factors in some instances. This is the most probable explanation of these cases.

TOXINS. The existence of a toxin, the product of the malarial parasite, is almost universally assumed by students of malaria. The grounds for this assumption may be briefly recounted as follows:

1. An analogy with other infectious diseases.
2. Immunity. This immunity is not absolute, but that a relative immunity to malaria exists there is no room for doubt.
3. The formation of an antitoxin. FORD'S⁸¹ experiments are nothing short of conclusive of the existence of an antitoxin.
4. Degenerative changes in the kidneys, liver, spleen and other organs, not otherwise explainable.
5. Blood changes, as anemia out of proportion to the number

of parasites and brassy degeneration, stippling and polychromatophilia of the red cells.

6. Increased toxicity of the urine and sweat.

7. The existence of coma in malaria without parasites or pigment in the brain.

8. The fever and its relation to parasitic sporulation.

9. Experimental proof. The negative results of GAULDI,⁸² MONTESANO,⁸² MANNABERG,²⁹ and CELLI⁵⁴ are devoid of weight against the convincing experiments of Rosenau, Parker, Francis and BEYER,⁸³ who demonstrated the existence of malarial blood of a poison capable of reproducing the symptoms of the disease when injected into the veins of other men.

INDIVIDUAL PREDISPOSITION AND EXTERNAL ETIOLOGICAL INFLUENCES. "We ought, then, in cases of pernicious fever, to seek in the conditions of the ground, whose quality is so different, and not in the quantity of the seed, the reason which shall explain to us the gravity of the disease."

The quality of the soil, in the sense so aptly employed by Homem, as a factor in the pathogenesis of pernicious malaria, has probably not receive the attention it deserves. This influence, in many instances, doubtless not only induces the attack but determines its type. Organs or systems enfeebled by antecedent ailments are apt to play the title rôle in the pernicious tragedy. Thus algid and choleraic attacks may be associated with a history of intestinal catarrh; the comatose and delirious cases, with a history of abuse of alcohol; the convulsive with epilepsy, etc. It is not improbable that some cases of dysenteric, cardialgic, syncopal, tetanic, cataleptic, paralytic, pneumonic, pleuritic, gastralgic and other forms described by the older writers may be similarly explained. MERCIER⁸⁴ goes so far as to say that all pernicious attacks are merely visceral complications.

Malarial subjects who are much exposed to the heat of the sun are liable to be stricken with pernicious fever, especially of the cerebral type. This danger is enhanced if to the solar heat are added fatigue, deficient or improper food or other hardships. Certain psychic states have causative significance. HERTZ³⁰ states that he has seen the localization of pernicious symptoms determined by injuries of the skull through a fall or a blow.

In addition to the four principal factors enumerated, congestion of viscera and parasitic obstruction of the hepatic capillaries

have been regarded as important. It is probable that they have little influence.

A feeble phagocytic activity was considered by Golgi as predisposing to pernicious attacks. In the present state of our knowledge it is impossible to define the relation of this function to perniciousness.

A consideration of the relative frequency with which the several factors are concerned in the pathogenesis of the various forms of pernicious malaria will necessarily be brief. In the comatose variety any of the four chief agents may take part; idiosyncrasy and external influences may unite with any of the other factors; an extraordinary number of parasites in the general circulation, without accumulations in the brain, is productive of coma probably because of the toxin. EWING⁸⁰ says that the majority of cases of comatose malaria coming to autopsy do not show a massing of parasites in the brain. He attributes these cases to general toxemia. However, a study of the autopsy records of MARCHIAFAVA and BIGNAMI⁵⁵ shows that in a great majority of their fatal comatose cases the parasites were markedly localized in the brain. DAVIDSON³¹ and RUGE²⁸ believe that almost always the cerebral capillaries are found filled with parasites in those who have died with coma.

Other pernicious cerebral forms are usually associated with parasitic localizations.

The algid variety, while possibly sometimes dependent on toxemia, is usually due to a massing of the parasites in the gastro-intestinal mucosa. This is explained by DAVIDSON³¹ as follows: "Experiments show that the alimentary tract is in closer connection with the cardio-inhibitory center than other parts of the body, and that irritation of this tract, if sufficiently powerful, will produce cardiac inhibition, with pallor of the surface and accumulation of the blood in the abdominal vessels. That the intestinal canal is the center of mischief in this form of pernicious attack will appear all the more probable if we observe the character of the disturbances so frequently associated with the algid condition—the cardialgic pain, the choleraic vomiting and purging, and the dysenteric discharges."

Other forms of pernicious malaria are probably due to localizations or to complications.

CLINICAL HISTORY, DIAGNOSIS, PROGNOSIS.

CEREBRO-SPINAL FORMS. The representative type of cerebro-spinal pernicious malaria is the comatose variety, which is, as well, the most frequent of all varieties.

Comatose malaria may make its appearance as the first manifestation of malaria, or, more commonly, after the lapse of one or more paroxysms, typical or irregular. Violent headache, stupid countenance and somnolence, interrupted by frequent sighing; with a mild grade of mental aberration and defective articulation and vision are not uncommon prodromata. These may, however, be so slight as to escape notice. The onset of cerebral symptoms may be with violent abruptness (the *apoplectic* form of some writers), or, as is most common, begins within a few hours after the commencement of the paroxysm, with somnolence, which gradually deepens into stupor and coma. It has occasionally happened that malarial coma has come on during natural sleep, the condition of the patient being discovered by accident. Convulsions may precede the coma, especially in children, or there may be extreme restlessness, gritting the teeth and jactitation. The cerebral symptoms may vary from marked drowsiness to the profoundest coma. The eyes may be closed or open (coma-vigil). The pupils are usually equal and dilated or contracted, but may be unequal and may or may not react to light. Strabismus is an occasional symptom. The face is congested in individuals recently attacked or pallid in older sufferers. The skin is at first hot and dry, perhaps slightly jaundiced; later it may be bathed with sweat. Petechiae are occasionally seen. Trismus may be present, but the extremities are usually completely relaxed, though sensation and motion are often not entirely abolished, as sometimes evidenced by resistance to hypodermic medication. Cases manifesting muscular rigidity and tonic contractures have been reported by SCHELLONG⁵² and by BROWN⁸⁵. Hyperaesthesia and muscular tremors are not infrequently present. The reflexes may be increased or diminished.

There may be twitching of the muscles of the face, usually confined to one side. Loud calls may not elicit response and shaking only groans and unintelligible utterances. The coma may be intermittent, running parallel with the temperature.

The fever in most cases varies from 101° to 103° , but may be subnormal or hyperpyrexial. The pulse is at first full and bounding; later small, rapid and feeble. Dilation of the right side of the heart may exist and an anaemic murmur may sometimes be heard. The respiration may be quiet, slow or rapid, or blowing and stertorous with Cheyne-Stokes characteristics late in the course. Edema of the lungs is an occasional late occurrence. Nausea and vomiting are seen early in the attack if they are present at all. The mouth and tongue are dry, the latter deeply coated. Herpes and sordes are sometimes noted. Hic-cough is an occasional symptom. The tongue when protruded may be drawn to one side. In cases of recent infection the spleen may be only slightly or not at all enlarged; in other cases it may be greatly enlarged, constituting a valuable diagnostic sign. The liver may be tender, but is usually not much enlarged. The evacuations of bowels and bladder may be involuntary or there may be retention of urine. The bowels are often constipated.

In favorable cases the coma gradually fades, consciousness slowly dawns, the temperature drops to or below normal, the pulse regains its normal characteristics and, save the physical weakness and a degree of mental hebetude, all is well with the patient.

In unfavorable cases the coma becomes absolute, the pulse becomes rapid, thready and irregular; the breathing is stertorous and of Cheyne-Stokes type, tracheal rattling appears, the face becomes cyanotic and death ensues from convulsions or from collapse.

The duration of an attack is from a few hours to a few days.

HERTZ³⁰ speaks of cases of "apparent death" arising in the course of comatose attacks. He describes these cases as follows:

"Under this form of pernicious intermittent must also be classed those cases of *apparent death* which may last from half an hour to four hours. Persons subject to such attacks may remain entirely conscious, seeing and hearing everything that occurs or is said around them, but unable to move or to utter a sound; or they may be entirely unconscious, respiration arrested, pulse and heart beat not to be recognized, and even the sharpest irritants applied to the body calling forth no signs of life until at the beginning of the sweating stage, the patient

comes to himself, and the various organs again slowly manifest their activity. TROUSSEAU reports the case of a man who had had fainting fits on two occasions in Algiers, and in a subsequent attack fell into this condition of simulated death. It was not until he had been carried into the post-mortem room that evidences of life were observed about him, whereupon he was returned to his bed and recovered under quinine treatment."

Relapses may occur after the apparently favorable defervescence of the symptoms. LAVERAN¹⁷ saw three successive attacks in a soldier. COLIN¹ reports several examples of pernicious attacks assailing the same subject repeatedly at intervals of 15 to 20 days. MAYER states that in a third of the cases another attack supervened in 8 or 10 days. More than three are very rare, but HOMEM⁷ records the case of a young student who died after having six pernicious paroxysms. It has long been maintained that the third attack is always fatal. It usually holds true that the successive paroxysms increase in severity and danger to the patient. In the interval the patient may be apathetic or may complain of headache. The relapse may appear in the form of a different type of pernicious paroxysm, as algid or choleraic, but such cases are very rare.

As intimated, the *apoplectic* form of pernicious malaria is merely a fulminant variety of comatose malaria. In these rare cases the onset is equally as sudden as in cerebral hemorrhage, whence the name. LAVERAN¹⁷, CARDAMATIS⁸⁶ and CRESPIN³⁴ are inclined to doubt the existence of this variety, but cases have been reported by MORRIS⁸⁷, DAVIDSON³¹, MAUREL¹⁵ and others. Ewing's case is remarkable. "The patient, while sitting up in bed smoking, three times in five days, suddenly became unconscious, his pipe fell to the floor, and he remained stuporous for three or four hours. At the end of that period he would wake up, at once pick up his pipe, and resume smoking."

Symptoms originating from the cerebellum are present in rare instances. Such are slow, monotonous speech, drowsiness, severe depression, and incoördination of voluntary movements.

MARCHIAFAVA and BIGNAMI⁴ describe as follows the interesting bulbar symptoms which occasionally present themselves: "When a physician unexpectedly encounters this disease he is easily inclined at the first glance to think that the case is one of a patient with bulbar paralysis who has become infected with

malaria, but this suspicion disappears after a careful examination and after seeing the gradual resolution of the symptoms. The chief symptoms are: difficulty in articulation, which may even reach anarthria, a weak and nasal voice, inferior facial paralysis, often of one side only, a half open mouth from which drools the saliva, a pendant lower lip, a dry and only slightly movable tongue, difficult or abolished deglutition. If the attack tends to a fatal issue, we have the added symptoms of sopor, a thready, intermittent pulse, labored and stertorous breathing, and clammy sweat. When, however, the result is favorable, the patient recovers from the more severe symptom as soon as the fever falls; the bulbar symptoms usually persist for some days, although in milder form; and then gradually disappear, the dysphagia going first, then the dysarthria and nasal voice, and the paresis of the lower part of the face. Two or three weeks may elapse before resolution is complete. If the malarial infection has not been properly treated, we shall have an exacerbation or even a return of the bulbar symptoms in the relapses. With these symptoms there are sometimes associated disturbances of equilibrium, which recall the staggering gait of cerebellar disease."

Cases in which hemiplegia occurs have sometimes been described as the *hemiplegic* form of pernicious malaria; cases with aphasia as the *aphasic* form. These two are not infrequently associated. Paraplegia is a very rare development in pernicious malaria.

A mild delirium is frequently present in the cerebro-spinal forms of pernicious malaria. When it is conspicuous it forms the so-called *delirious* type. In this, probably more than in any other form, do predispositions have a casual part, especially alcoholism, nervous predisposition, mental fatigue and exposure to solar heat. Delirium in this condition may vary from quiet to maniacal. Cases resembling rabies have been designated *intermittens hydrophobica*, and are thus described: "Violent maniacal delirium, with a frequent pulse, red, glowing face, and clonic spasms of the muscles of deglutition on drinking, or even at the sight of water; these spasms then pass to the muscles of the face, the eyes and the neck, and finally to those of the entire body, a disposition to bite being at the same time developed."³⁰

Convulsive or *eclamptic* pernicious malaria is a variety of the

comatose type in which convulsions are a prominent feature. It is especially common in children. The convulsions may be confined to certain muscle groups or may be general. In one of my cases the little patient had twelve convulsions in an hour. Epileptiform convulsions have been described, but it is probable that most of these cases are complicated with true epilepsy as the case of MARCHIAFAVA and BIGNAMI⁵⁵.

Cases in which the symptoms resemble more or less closely those of tetanus constitute the *tetanic* type of some writers. These cases are said to have been relatively frequent in the French campaign in Madagascar⁶. ZIEMANN⁶⁹ records a typical case. The most prominent symptoms are usually trismus and opisthotonos; emprosthotonos and pleurosthotonos are but rarely observed.

Occasionally *amaurosis* arises in the course of a comatose attack. It may be transient, or, in rare instances, permanent. In the only case occurring under my observation vision began to improve at the end of the attack, but was not fully restored until after several weeks. According to PONCET⁸⁸ the persistence of amblyopia in these cases is due to optic neuritis, peripapillary edema, extravasation of leucocytes, plugging of retinal and choroidal vessels by parasites or pigmented leucocytes, and consequent multiple hemorrhages.

A rare form of pernicious malaria, the *ataxic*, has been described particularly by ANGELLINI and TORTI⁸⁹. The principal symptoms are scanning speech, dysarthria, weakness of lower limbs, vertigo, unsteady gait with a disposition to fall forward, muscular tremors and exaggerated reflexes. MAUREL¹⁵ records twenty-two cases, but it appears that some of these cases at least do not belong to the ataxic type.

MANSON⁵ thus describes the so-called *ardent* fever: "In the course of what seemed to be an ordinary malarial attack the body temperature, instead of stopping at 104° or 105° Fahr., may continue to rise, and passing 107°, rapidly mount to 110° or even to 112°. The patient, after a brief stage of wild, maniacal, or, perhaps, muttering delirium, becomes rapidly unconscious, then comatose, and dies within a few hours, or perhaps within an hour of the onset of the pernicious symptoms." Both the cases of this type observed by HOMER⁷ ended fatally.

Typhoid pernicious has been most carefully studied by BIL-

LET¹¹. In these cases the clinical picture is almost identical with that presented in typhoid fever. The temperature is periodically intermittent, or, as is more common, remittent, and usually ranges from 101° to 103°, but may reach 106°. There are headache, backache, rapid pulse, torpid digestive tract, sordes, splenomegaly, apathy and stupor. There may be diarrhoea, or constipation and bilious vomiting occurs in some cases. The abdomen is usually tympanitic and there may exist tenderness and gurgling in the right iliac fossa. Epistaxis is frequent. Incoherent speech, delirium and incontinence of urine and feces are symptoms of severe cases. All of Billet's forty cases showed the presence of malarial parasites and a large mononuclear leucocytosis and an absence of rose spots and the Widal reaction. The average duration was four or five days.

THORACIC FORMS. The immunity of the organs of the chest to localizations of the malarial parasites and to the effects of their toxins is remarkable. Indeed, the thoracic forms are much rarer than the records would import, for the older writers especially were prone to attribute any complication that might present itself to the effect of the mysterious malarial poison.

EWING⁸⁰ has minutely recorded a case in which the autopsy showed an enormous number of parasites in the capillaries of the heart muscle. The symptoms referable to the heart were feeble pulse, 124 to the minute, and very feeble heart sounds on auscultation. The patient was comatose. BENVENUTI⁷⁸ has reported a case in which the capillaries of the myocardium, brain and kidney were filled with infected red cells. The principal symptoms were coma and dyspnoea.

Formerly cases of *pneumonic* pernicious malaria were more frequently reported than at present. Since more exact methods of observation have come into use it is certain that many of these cases were complicating lobar pneumonias. That the malarial parasite is unable to cause true inflammation of lung tissue is now widely recognized, and was maintained by COLIN⁵⁵, JACCOUD⁹¹, ROUX², and MARCHIAFAVA and BIGNAMI⁵⁵. Nevertheless grave symptoms referable to the lung, and more or less resembling pneumonia, may arise in malarial infections. LAVERAN¹⁷, who doubts the existence of a *pneumonic* pernicious, admits that in certain patients attacked with intermittent fever, there may be observed, with each attack, pulmonary congestion, accom-

panied with subcrepitant rales, which may lead to a belief in the existence of a pneumonic intermittent. BACELLI⁹² proved the existence of a group of cases nearly resembling pneumonia in symptomatology. The characteristic cough, dyspnoea and pain in the side are present. There may be moderate dullness and coarse, sonorous and sibilant rales heard over the portion of the lung involved. Other writers describe intermittent lung symptoms and signs met in cases of pernicious malaria. LE DANTEC⁶ records the following case, occurring in the person of his friend, Dr. Grosset, who, after several paroxysms of intermittent, was taken in course of an attack of fever with dyspnoea. Percussion showed incomplete dullness throughout the entire extent of the chest. Auscultation revealed crepitant rales. The face and finger nails were cyanosed, the intelligence was unimpaired, but the peripheral sensibility had almost disappeared. The chest was covered with cupping-glasses and several hypodermic injections of quinine were given. This alarming condition lasted almost twenty-four hours, when, at the moment a fatal issue was expected, the sensibility returned and every trace of pulmonary congestion disappeared as if by magic. Cases presenting profuse hemorrhages from the lungs and nose have been recorded but rarely.

The pathogenesis of this condition is not known, as there have been insufficient post-mortems. From analogy with findings in other forms of pernicious malaria these cases must be attributed to accumulations of parasites in the pulmonary capillaries. GRIESINGER⁹³ early compared the filling up of the lung that takes place in these cases to the enlargement of the spleen.

ABDOMINAL FORMS. The representative type of abdominal pernicious malaria is the *algid*. The reasons for classing this type as an abdominal form have been briefly stated when considering the pathogenesis of the different varieties. The picture presented is that of abdominal shock; it is peritonism minus the peritonitis.

TORTI believed that the algid attack was merely the intensification of the cold stage of a malarial paroxysm. But there are essential differences. First, the algid attack almost always occurs during the febrile period and does not correspond in time to the first stage. Secondly, in the cold stage of the ordinary paroxysm the patient experiences a sensation of chilliness; in

the algid attack the patient feels that he is "burning up," while the skin feels cool to the observer. The algid symptoms may appear insidiously, but much more frequently supervene after the course of one or more simple paroxysms. Usually the first symptoms that attract the attention to the condition of the patient are the bad pulse and cold surface. Soon the Hippocratic facies is assumed. The eyes are deeply sunken and surrounded by dark circles; the nose appears sharp, the alae nasi dilate with respiration, the tip of the nose and the ears are icy cold. The temples and cheeks are hollowed, the cheek bones project, the pupils are dilated, the conjunctivae bluish white, the eyes have a peculiar anxious expression and the breath is cool. The skin is pale, having the appearance of absolute bloodlessness rather than that of cyanosis. The surface of the body is bathed with a clammy sweat, is cold, and gives the sensation to the hand of handling a catfish. The fingers and toes often have the shrunken appearance of the washerwoman's hand. The prostration is extreme and the voice is low, weak and cracked. The patient complains of burning heat within and begs piteously for cold drinks, which are as a rule immediately rejected by the stomach. The intelligence remains clear and occasionally "the patient, overcome by sad apprehensions, considers himself lost, bewails his situation, but is not delirious," though usually he is indifferent to his peril. The temperature may be subnormal or slightly elevated, seldom reaching 104° . The pulse is rapid, filiform, of low tension and often intermittent. Later it usually becomes imperceptible at the radial. The heart sounds are extremely feeble. The respiration is very rapid, superficial and frequently interrupted with deep sighs. The tongue is tremulous, cold and usually moist and smooth. Vomiting is a common symptom. The bowels are sometimes constipated, but often loose. The abdomen may be slightly tympanitic, or scaphoid and tender, especially in the upper half. The urine is scanty, highly colored and of high specific gravity. The duration of the attack is short, rarely longer than twelve hours after the onset of algidity. In fatal cases the symptoms progress rapidly and the patient dies as if in peaceful sleep. In favorable cases the character of the circulation and respiration improves, the body warmth is gradually restored, the patient ceases to complain and convalescence is impeded only by the extreme weakness.

When, in addition to the symptoms of algidity already de-

tailed, there exist symptoms simulating true cholera, there is the variety of algid malaria usually spoken of as *choleraic* pernicious. The onset is with profuse diarrhoea and vomiting. The stools are thin and watery and often rice-water like. There may likewise be shown the muscular cramps of the lower limbs frequent in cholera. The temperature is usually elevated and pains in the abdomen and precordia and singultus may be experienced. The urine is usually scanty and may become suppressed.

The condition of algor with which drenching diaphoresis occurs constitutes the so-called *sudoral* or *diaphoretic* form of pernicious fever. These sweats, which are so profuse that not only the clothing of the patient but also the bed clothes are saturated, usually supervene toward the close of a paroxysm. The celebrated TORTI, who was himself the victim of such an attack, says that he was just congratulating himself upon escaping the fever when the abundant sweats occurred to convince him that his condition was critical.

In the course of an algid access *syncope* occasionally occurs when any exertion, even the slightest, is attempted, or when the patient's head is lifted from the pillow. This dangerous symptom usually comes quite unexpectedly and if the patient survives the first onset, a subsequent one may rapidly prove fatal.

The *gastralgic* or *cardialgic* type is characterized by excruciating pain in the abdomen, especially the epigastric region, or in the precordia. The pain is often so intense that the patient doubles up and rolls in agony upon the bed. The abdomen is tender and vomiting is a common symptom. There may be hematemesis, sometimes profuse. Diarrhoea and singultus are occasional symptoms.

While the existence of *dysenteric* pernicious malaria has been denied by COLIN²⁶ and more recently by KANELIS and CARDAMATIS¹² the frequent occurrence of severe dysenteric symptoms, due solely to malarial infection, has been definitely demonstrated by CRAIG⁹⁴. The attack may follow other forms of abdominal pernicious or may come on suddenly. There are frequent actions of bloody mucus, violent tenesmus, colicky pains in the abdomen, elevation of temperature and sometimes emaciation. Algid symptoms are not common. Occasionally abundant hemorrhages from the bowels occur. They may prove rapidly fatal, especially if the patient is already markedly anæmic.

Icterus and bilious vomiting are not rare in malaria. As a

rule these are not grave symptoms, but there are cases in which their persistence and intensity form a complex of symptoms described as *bilious* pernicious malaria. The fever is usually high, nausea constant, icterus marked, and vomiting of bile distressing. Bile is present in the urine, often in quantities, and sometimes albumin. Epistaxis and hematemesis have been noted. The epigastrium is often painful and singultus may add to the discomfort of the patient. Toward the end of the severe cases there are apathy and carphologia and the scene usually closes with delirium and coma.

WATON⁹³ observed a case with symptoms resembling those of peritonitis. GILLOT⁹⁵ treated three cases in which the clinical picture was identical with that of acute peritonitis. One case which he diagnosed as perforation due to typhoid ulceration was operated upon. The operation proved a mistaken diagnosis. The blood was examined, malarial parasites found, and the patient recovered promptly after the subcutaneous injection of one and a half grams of quinine.

WOLF⁹⁶, CHAMBERLAIN⁹⁷ and CRAIG⁹⁸ report cases presenting symptoms which would lead to a diagnosis of appendicitis. FORD⁷⁹ records five such cases, one of which was operated upon and the appendix found to be healthy.

ROSS and DANIELS⁹⁹ performed an autopsy on a man who was not supposed to have died of malaria, and found a hemorrhagic pancreatitis with extensive massing of parasites in the pancreas. Parasites were also very numerous in the capillaries of the stomach and intestines and these organs showed extensive necrosis.

The urine is generally highly colored. The amount varies inversely with the quantity of sweat, bowel movement and vomited matter; the specific gravity varies inversely with the amount. Early in the attack albumin may be absent, though later it is often present in large amounts together with numerous tube casts.

The blood, in various forms of pernicious malaria, shows besides parasitic findings previously mentioned, a pronounced reduction of red cells averaging a half to one million per paroxysm. Polychromatophilia of red cells may be observed. Contrary to the case of simple malaria there is usually a pronounced leucocytosis. There may be as many as 35,000 per cm. Thayer observed a case of the algid type in which they were 50,000 in number. The differential formula usual in malaria, the relative increase of large mononuclear elements, is maintained. Accord-

ing to BILLET¹¹ the average of these cells is 10-15% ; in nine of his forty cases it varied from 20-25% and in one case they existed in the proportion of 30%. Great numbers of these cells were pigmented.

COMPLICATIONS AND SEQUELS. The most frequent of these are nephritis and nervous and mental disorders.

It is not unusual for nephritis to arise in the course of a pernicious attack. This usually subsides during convalescence, but may persist in a subacute or chronic form.

The nervous complications occur most frequently following the cerebro-spinal forms of pernicious malaria. BUSQUET¹⁰⁰ reports a case where the patient, who had had comatose malaria, suffered from girdle pains, paresis of right arm and leg, with rhythmical tremors and incontinence of urine and feces. SEGARD¹⁰¹ observed acute mania with erotic tendencies lasting three days. MINE¹⁰² records six cases of motor aphasia lasting from eleven to forty-two days. MAUREL occasionally observed enfeebled memory and persistence of the paralysis following the ataxic variety. CATRIN¹⁰³ writes of peripheral neuritis as a complication of some cases. He cites the case of a patient who had motor and sensory disturbances of both legs. MARCHIAFAVA and BIGNAMI⁵⁵ give the history of a case resulting in psychical weakness and excitability, hesitation in speaking, and enormous exaggeration of the reflexes, recalling the phenomena of disseminated sclerosis. CARDAMATIS⁸⁶ has observed paralysis and mental troubles as sequelæ of comatose cases. Acute anterior myelitis with atrophy of some of the muscles of the lower limbs, especially the triceps, is recorded in one of LAVERAN'S¹⁷ cases.

This writer observed another case in which hemiplegia of the right side and complete asphasia persisted for a long time. KELSCH and KIENER²⁶ had a case in which delirium continued about a week. MANSON⁵ states that permanent psychical disturbances succeed certain of the cerebral forms of pernicious fever.

DIAGNOSIS. We would indeed be in a sad plight had we no diagnostic criteria other than those enunciated by TORTI¹⁰⁴. These are (1) the condition of the pulse; (2) the condition of the urine, and (3) the paroxysmal succession of the symptoms. Even the following marks of HOMEM⁷ leave everything to be desired in many cases:

1. The rapidity with which the symptoms develop and acquire their maximum intensity.

2. The singular want of harmony noted in the symptoms, the unusual manner of their grouping, such that they can be referred to no fixed disease.

3. The gravity of the symptom or symptoms denoting perniciousness.

4. The rapid enlargement of the liver, and sometimes of the spleen as well.

5. The splenic pain, really a splenalgia, which appears independent of the enlargement of the spleen, and is revealed when the left hypochondrium is compressed beneath the last rib.

It is only since LAVERAN'S revolutionizing discovery that the diagnosis of pernicious malaria has been reduced almost to exactitude. Cases have already been recited where the parasites were scanty or even missed in the blood, but these are only rare exceptions. In the immense majority of cases examination of the peripheral blood will reveal the presence of the organisms. The value of this is inestimable and is paralleled only by the importance of making blood examinations in all cases. It may safely be said with CRAIG⁵¹ that hundreds of lives have been sacrificed to pernicious malarial fever which could have been saved had an examination of the blood been made. It is not extremely uncommon in our cities for subjects of pernicious attacks, found in coma, to be taken to the police stations instead of to hospitals, and the true condition not suspected until the patients fail to "sober up" in due time, when it is usually too late for treatment to avail.

Negative examinations of the peripheral blood may in desperate cases possibly justify risking the dangers of splenic puncture.

Diagnosis by exclusion may render great assistance, but the heroic administration of quinine must be regarded rather as a life-saving measure than as a therapeutic test.

In cases showing the presence of parasites complications must be rigidly excluded. In some cases this is attended with difficulties.

In comatose malaria, besides the evidences obtained by an examination of the blood, a history of exposure to, or attacks of, malaria, the general appearance and age of the patient, the absence of atheroma, the early elevation of temperature, and per-

haps the enlargement of the spleen and slight jaundice, should exclude cerebral hemorrhage. The differentiation of malarial coma from sunstroke is often hard; in fact, the two not infrequently co-exist, in which case it may be impossible to apportion the etiological share of each in the clinical picture. CARDAMATIS⁸⁶ states that in this type of pernicious malaria coma is the dominating symptom, while in sunstroke are observed coma, convulsions, delirium and hyperpyrexia. Uremic coma may simulate that due to malaria. Unfortunately the urinalysis throws no light on the diagnosis, as in both conditions we may find albumin and casts. The blood examination, the temperature and the anamnesis serve to make the diagnosis. For the differentiation of alcoholic from malarial coma the blood examination is essential. The history may be of value, but the odor of the breath may be misleading. To discriminate between malarial coma and diabetic coma the presence of the parasites on one hand and of glycosuria on the other are sufficient. In differentiating between the various comas with reference to malaria two points should be remembered: First, that comatose malaria may occur in persons with the odor of alcohol on the breath; and, secondly, that coma from causes other than malaria may attack malarial cachectics. To distinguish epilepsy, opium poisoning, tetanus and meningitis from pernicious malaria should rarely present difficulties if the blood is examined. The following table of differential features of amblyopia due to quinine and to malaria is borrowed from MANSON⁵:

QUININE AMBLYOPIA.

HISTORY—Quinine taken in large doses, not less than thirty grains.

ONSET—Sudden, accompanied by deafness; both eyes are affected.

PUPILS—Widely dilated and whilst loss of vision continues, they do not react to light.

VISION—Completely lost for a time.

OPHTHALMOSCOPIC APPEARANCES—A white haze over fundus; cherry-red spot at macula; optic disc pale; retinal vessels markedly constricted.

TERMINATION—Usually some permanent defect in the field of vision or in color vision. Central vision recovers first; optic disc is unusually white, and retinal vessels small.

TREATMENT—Stop quinine. Amyl nitrite has been recommended to induce dilation of retinal vessels.

MALARIAL AMBLYOPIA.

HISTORY—Quinine may have been taken, but not necessarily in large doses.

ONSET—Not usually sudden, but it may be so if hemorrhage has occurred in the macular region. There is no deafness, and both eyes are not necessarily affected.

PUPILS—React to light.

VISION—Never completely lost.

OPHTHALMOSCOPIC APPEARANCES—There is optic neuritis; optic disc is of characteristic grayish red color; retinal hemorrhages and sometimes vitreous opacities.

TERMINATION—Some cases recover completely; in others greater or less permanent defect of vision remains.

TREATMENT—Give quinine.

Algid attacks sometimes resemble perforation of typhoid or gastric ulcers or rupture of the spleen. The microscope and the local symptoms should render the diagnosis certain. The cases resembling appendicitis and peritonitis have been mentioned; here again the microscopic examination of the blood may save lives. In countries in which cholera is endemic the diagnosis between this disease and the choleraic type of pernicious malaria was formerly difficult or impossible. LAVERAN's discovery has removed this difficulty and rendered possible a diagnosis of the utmost importance. The finding of the hematozoa differentiates the hemorrhagic, bilious and typhoid types from typhoid and yellow fevers.

PROGNOSIS. The prognosis is extremely grave. It depends upon the physical condition and age of the patient, the type and severity of the attack, and the promptness and efficiency of the treatment. Anæmia from previous attacks of malaria or other causes, alcoholism or organic disease of important viscera add to the gravity of the case. The cerebral types are less serious in the young and vigorous, very fatal in the aged. As a rule patients seen early and treated skillfully and energetically have a better chance for life, but many cases end fatally in spite of the best and most timely treatment.

The number of parasites in the peripheral circulation is not always a reliable guide as to the severity or progress of the attack. With apparent amelioration of the symptoms the physician should be circumspect in his prognosis and bear in mind the possibility of further paroxysms.

In the writer's opinion the algid type is the most lethal, the typhoid and dysenteric least so, though this is not exactly in accord with COLIN⁷³, who arranges the types according to the following descending scale of gravity: Syncopal, algid, cardialgie, delirious, comatose, icteric, choleraic. SCHELLONG⁵² regards the comatose as the most dangerous and LE DANTEC⁶, the delirious and algid.

PARRY¹⁰⁵ states that average mortality of pernicious malaria is one out of every eight cases; WHARTON¹⁰⁶ estimates it as one of every twelve or fifteen; HASPEL¹ and BORIUS²⁵, one-third; PAMPOUKIS¹, 21.4-25.4%; LE DANTEC⁶, 20-50%, and CRESPIEN³⁴, 20-70%. The algid type is said by PAMPOUKIS¹ to be fatal in 55.5% of cases. CARDAMATIS⁸⁶ states that the comatose variety is fatal in

20-40%; BERGEAND¹⁰⁷ believes the mortality of this type to be 50%.

The following list of 18,529 cases compiled from the literature shows a mortality of 27.6%. The first column of figures shows the number of cases, the second, the number of fatalities:

Laveran ¹⁷	104	53	Maillot ¹¹¹	7	6
Bailly ¹⁰⁸	886	341	Theophanidis ¹¹¹	5	2
Nepple ¹	14	6	Cardamatis ¹¹²	3	2
Antonini and Monard ¹	39	9	Pampoukis ¹⁰⁷	52	20
Maillot ¹	186	38	Billet ¹¹	40	2
Grall ¹⁰⁹	117	75	Ségard ¹⁴	24	15
Burot and Legrand ¹⁸	210	142	Maurel ¹⁵	156	77
Smart ¹¹⁰	16209	4164	Caccini ²⁴	135	56
Travers ¹⁹	260	81	Maritirano ²⁴	6	3
Martirano ¹⁶	19	9	Charity Hosp., N. O. ¹¹³	8	6
Pezza ²¹	2	1	Neer ⁴⁴	3	3
Tanzarella ²¹	31	8			
Thayer and Hewetson ²³	3	2	Total	18,529	5122
Plehn ⁴⁰	10	1			

Six hundred and eighty-nine cases of specified type give the following respective mortalities:

	Comatose		Delirious		Algid		Typhoid		Ataxic	
Maillot ¹	77	14	61	12	48	12				
Schellong ⁵²	7	6								
Plehn ⁴⁰	10	1								
Maillot ¹¹¹					7	6				
Theophanidis ¹¹¹					5	2				
Cardamatis ¹¹²					3	2				
Pampoukis ¹⁰⁷	52	20								
Billet ¹¹							40	2		
Maurel ¹⁵	279	103			78	23			22	17
Neer ⁴⁴	3	3								
Total	428	147	61	12	141	45	40	2	22	17
Mortality	34%		20%		32%		5%		77%	

MORBID ANATOMY.

The pathognomonic anatomical feature of malaria is intravascular melanin, which is a product of hemoglobin converted through the biological agency of the malarial parasites. Melanin occurs in the tissues also, but here there is some doubt as to its origin. It is brownish black in color, occurs in fine grains, coarse particles, or in lumps, does not yield the reaction for iron, and is insoluble in acids, but is readily dissolved by ammonium

sulphide. This should not be confused with hemosiderin, which is a chemical derivative of the hemoglobin of broken down red blood cells, is yellowish in color, responds to the reaction for iron, is insoluble in acids, alkalies, alcohol and water, and exists especially extravascularly. It is regarded as a result of prolonged hemoglobinemia following severe or chronic infections.

The general plan of distribution of melanin may be thus stated: In the blood current it may exist free, or more commonly is contained with the phagocytes and the red cells infected with pigmented parasites and is more abundant in the capillaries than in the larger vessels. In the viscera it is oftenest seen in the spleen, bone marrow, brain and liver, especially in the endothelial cells, but in the spleen and bone marrow it exists also outside the vessels and either between or within the cells proper to these tissues.

The distribution of the parasites varies according to the type of the attack; it has been shown that the latter depends largely upon the localizations of the parasites. They are usually abundant in the splenic blood irrespective of the form assumed by the attack. It occasionally happens that death supervenes, notwithstanding a progressive diminution of the parasites so that the latter may be scanty or even absent. In the spleen are found not only schizonts, but also numerous sexual forms which are likewise usually found in the bone marrow and even in the liver, but in the brain the gametes are conspicuously few. Parasitic development is checked almost immediately upon the death of the host.

The *spleen* is always more or less enlarged, though perhaps slightly so in acute cases following recent infections. The edges are often rounded, the organ tending to lose its characteristic contour and to assume a spherical shape. The color varies from reddish brown to almost black, being darker in old malarials. In consistence it is usually softer than normal, often semifluid, sometimes resembling a bag of pulp. The capsule is thinned, occasionally adherent to the adjacent organs, and is very liable to rupture. The cut surface is dark in proportion to the age of the infection. The pigmentation is occasionally uniform and the tissues hardly distinguishable, though as a rule the Malpighian bodies stand out distinctly. The venous sinuses are often dilated. Microscopically there is enormous cellular hyperplasia

with distension of Mall's pulp cords. The spleen cells are everywhere intercalated with red blood corpuscles, a large per cent of which are infected. The parasites may be in the same or in different stages of development. The pigment is contained in the large mononucleated leucocytes, endothelial cells and giant cells. The latter contain also red cells, parasites and even small phagocytes and are most abundant in the splenic vein. They sometimes show evidence of necrosis. The Malpighian bodies and the fibrous trabeculae are usually unpigmented. Mitotic cells may be found in the pulp and in the Malpighian bodies. The circulation may be so obstructed that edema, interstitial hemorrhage and cellular necrosis may occur.

The *liver* is generally enlarged, but in a less proportion as to frequency and size than the spleen. The color is usually a dirty brown, the surface is sleek, and the form is preserved. The consistence may be normal or somewhat diminished. The parenchyma presents a reddish brown color after recent infections and the cut surface drips blood. The gall bladder is often distended with a quantity of dark inspissated bile. Microscopically parasites are not so abundant as in the spleen. Pigment is found in the vessels, especially in the blood capillaries. Here are found also altered parasites, melaniferous leucocytes and large endothelial cells containing coarse grains of pigment. The macrophages are sometimes of an enormous size. The pigmented endothelial cells are swollen and the capillaries are not infrequently entirely obstructed with pigmented cellular elements. The hepatic cells do not contain melanin, but are frequently charged with hemosiderin, and may show evidences of cloudy swelling, atrophy or necrosis. Karyokinesis is occasionally noted. Areas of focal necrosis have been described.

The *kidneys* on gross inspection show few changes; they may be slightly enlarged and hyperemic. Microscopic examination shows a marked pigmentation of the Malpighian corpuscles, together with degenerated tubular epithelium. While the epithelium of the tubules may be healthy, it often shows cloudy swelling and necrosis. In the straight tubules there may be casts of various sorts. Melanin is found in the glomeruli, less often in the tubules. The cells may contain hemosiderin granules. Parasites are rare in the glomerular vessels, but may be found in the intertubular capillaries. EWING'S⁷⁷ case with massing of the parasites in the

renal capillaries has been mentioned. A true glomerulitis has been found in cases of the algid type.

In cerebral cases the only variation from the normal condition of the *stomach* and *bowels* may be only a slight pigmentation. In fatal cases of the algid and choleraic forms the gastro-intestinal tract may contain a bloody fluid and the mucus membrane may be swollen, hyperemic, pigmented, necrotic or ulcerated. The follicles and Peyer's patches may be hypertrophied and prominent. Microscopically there is vivid injection, parasitic and pigimentary thromboses of the capillaries, hemorrhagic points and necrosis. The peritoneum is usually normal.

Macroscopically the *lungs* may show nothing abnormal save probably slight results of hypostasis which in some cases may be cadaveric lesions. Occasionally there are hemorrhagic areas. Microscopically neither pigment nor parasites are so evident as in certain of the other organs. The capillaries are congested, sometimes thrombosed, and contain infected erythrocytes, phagocytes, which often show signs of degeneration, and macrophages. The capillary epithelium may be swollen, but is only occasionally pigmented. The pleuræ show nothing abnormal.

The *heart* muscle is ordinarily pale and flabby, but the muscular fibres do not usually afford degenerative signs. The capillaries may contain parasites in greater or less number and the endothelium may be swollen. Cases in which the parasites are very numerous in the cardiac capillaries, such as that of EWING⁸⁰, are very rare.

In cerebral cases the meninges of the *brain* are deeply hyperemic; an excess of serum is found in the meshes of the pia, in the ventricles and at the base of the brain. The cerebral substance is commonly darkly pigmented and congested and may show hemorrhages, usually punctiform, occasionally larger. The hemorrhages occur oftener in the cerebrum, but may be present in the cerebellum. In the abdominal forms the brain may show but few pathological changes. Microscopically in the cerebral cases the capillaries are seen to be filled, even to occlusion with pigment, parasites and phagocytes, the latter in the same or in different stages of schizogony; gametes are seldom found. In some instances nearly every red cell contains one or more parasites. Localizations of parasites are found not only in the cerebrum, but also in the cerebellum and medulla. The capillary en-

endothelium may be swollen, pigmented and undergoing fatty degeneration. Secondary changes such as perivascular exudation, hemorrhages and necrosis are not uncommon results of thrombosis. Degenerative changes in the ganglion cells have been detected.

The *bone marrow* is of a dark color approaching that of the spleen, and sometimes diffluent. Microscopic examination reveals hyperemia, the capillaries being engorged with pigmented parasites and giant cells clinging to the vessel walls. The parasites exist as free spores, schizonts, which are frequently sporulating, and gametes in large numbers. Extravascular parasites and free pigment are also found.

TREATMENT.

It has been shown that the proportion of pernicious to benign malaria is about 1 to 90, and that about 31% of deaths from malaria are due to pernicious malaria. In the registration area of the United States during 1906 there occurred 1,415 deaths from malaria. If 31% of these deaths were due to pernicious malaria the latter caused more than four times as many deaths as did smallpox in this area during the same period. Pernicious features in malaria are almost as common as perforation in typhoid fever and are three times as frequent as puerperal eclampsia, and seven times as frequent as placenta previa in obstetric practice. These facts, together with a mortality of 27.6%, should be conclusive as to the importance of prophylaxis. The prevention of pernicious malaria may be briefly stated as, first, the prophylaxis of malaria; secondly, the prompt treatment of all malaria attacks.

The only drug promising any hope of cure in the treatment of pernicious malaria is the alkaloid of the "divine bark." Quinine should be administered promptly in all cases without delaying for "preparatory" treatment.

The method of giving the drug is of the utmost practical importance. The intra-tracheal method of JOUSSET DE BELLESME⁴⁶ and the subarachnoid of JABOULAY⁴⁶ are mentioned only as therapeutic reminiscences.

There are certain cases apparently on the border line between benign and pernicious malaria of the cerebral type which may cause hesitation as to the mode of administration. In these cases, usually in children, the patients, though stupefied, or even semi-

comatose, can be aroused and made to swallow and usually retain the medicine. In such cases, if the patient can be watched, the quinine may be given by solution in the mouth. If vomited or if the symptoms do not rapidly improve, the drug in dilute solution should be injected intramuscularly. Where the injection mode is chosen it is advisable to supplement this with oral administration of the solution where it can be swallowed, and even the rectum may be employed also.

Quinine was used hypodermically at least as early as 1863, when BOURDON⁹¹ employed the sulphate dissolved in water with tartaric acid. Later this salt was dissolved in water acidulated with sulphuric acid. Bad results were common. ARNOULD¹¹⁴, in 1867, reported, in 95 patients thus injected, 2 indurated nodes. 4 eschars and 15 abscesses. In 1888 BEURMANN and VILLEJEAN¹¹⁴ introduced for hypodermic use the bimuriate in the following formula, which is still widely employed:

Quinine bimuriate	5 gm.
Distilled water to	10 cc.

KÖBNER¹ recommends:

Quinine hydrochlorate	5-1 gm.
Glycerine	
Distilled water, aa.	2 gm.

GRIMMAUX¹:

Quinin. hydrochlorico-sulph.	5 gm.
Aqua dest.	6 cc.

KLEIN²⁶:

Quinin. hydrobromat.	2 gm.
Sulphuric ether	12 cc.
Alcohol, q. s.	20 cc.

TRIULZI¹ added antipyrine to promote solution and diminish pain.

Quinin. muriat.	3 gm.
Antipyrine	2 gm.
Aqua	6 cc.

VINCENT and BUROT²⁶:

Quinin. muriat.	3 gm.
Analgesin	2 gm.
Aqua	6 cc.

GAGLIO¹:

Quinin. hydrochlorat.	3 gm.
Urethane	3 gm.
Aqua	5 cc.

The addition of cocaine has been also recommended to lessen the pain.

The most suitable salt of quinine for injection is unquestionably the bimuriate. The tablets of bimuriate of quinine and urea are convenient and insure accurate dosage.

The advantages of giving quinine by the needle in pernicious malaria are obviously being able to administer it to patients unable to swallow or to retain it, and the certainty and promptness of absorption. Nevertheless, these great benefits are somewhat discounted by bad results which sometimes appear. Formerly tetanus was to be feared. BARTHOLOW¹¹⁵ mentions several such cases reported from New Orleans, and two occurring in one regiment of the British Indian Army. VINCENT¹¹⁶ in a late report recalls the numerous cases following the subcutaneous use of quinine. McCAMPBELL¹¹⁷ speaks of a fatal case of tetanus shortly following a hypodermic injection of the hydrochlorate of quinine, though the experiments of this writer fail to corroborate those of VINCENT to the effect that the injection of quinine favors the development of the tetanus bacillus. In the late French campaign in Madagascar, six cases of tetanus subsequent to hypodermics of quinine came under observation²⁸. But there are other consequences which, while not so deadly, are more commonly met. I refer to nodules, necrosis, sloughing and abscess formation. PLEHN⁶⁶ has frequently seen necroses and abscesses result from hypodermics of quinine. THAYER⁵⁰ says there is always danger of subsequent abscess or necrosis. LAVERAN¹⁷ states that injections made into the skin often give rise to eschars. MANSON¹¹⁸ has often seen induration, if not abscess, follow the hypodermic injection of quinine, conducted in the ordinary way. BONNETTE¹¹⁴ and LEDANTEC⁶ say that in spite of the greatest aseptic precautions eschars and abscesses will sometimes result. CRAIG¹¹⁹ has observed abscesses in about 20% of the cases and often had nodular elevations at the seat of puncture which persist for some time. GROS¹²⁰ and TYSON¹²¹ have abandoned the method on account of the frequency of abscess formation.

These results, however, should not prevent the use of quinine injections in the treatment of pernicious malaria, as such effects are in a great measure preventable. To this end there are three measures of importance: First, asepsis; secondly, dilute solutions, and, thirdly, deep injections.

The first is at the present day probably the least often neglected, as most physicians realize the importance of sterilization and a spoon and a few matches are sufficient to effect it on the part of the solution and needle, and soap and water are almost omnipresent.

The necessity of employing a dilute solution has been all but ignored. Nearly all writers on the subject lay great stress on the need of asepsis, but with few exceptions even mention the evils of too concentrated solutions. Strong solutions of quinine injected into the tissues cause a wall of necrosis around the solution preventing absorption and paralyzing phagocytosis, resulting, even if the solution is sterile, in nodes or ugly chemical sloughs. It is in all probability this chemical irritation of the cells which allows of bacterial infection following the injection of solutions not properly sterilized. Witness the frequency with which unsterilized solutions of morphine and other drugs are given without the slightest bad consequence.

For injection purposes the following formula is most suitable:

Quinine bimuriate	1 gm. (grs. xv)
Water	10 cc. (drs. iiss)

As much of this as needed may be injected in one or several locations.

The solution should not be injected hypodermically, but *intramuscularly*, since in the latter location the injection is more certainly absorbed, is less apt to cause induration and abscess, and is less painful. In some cases of pernicious malaria the superficial circulation is very poor, absorption correspondingly inadequate, and necrosis almost inevitable, if the quinine is not deeply injected. In a case of algid malaria in my practice where the quinine was given hypodermically the site of injection began to turn blue within ten minutes and was almost black within two hours.

The initial dose should ordinarily be fifteen grains. Afterwards from five to ten grains should be injected every six or eight hours as long as the symptoms demand it. For children under five years the first dose may be a grain and a half for each year of age. The statement of HOMER⁷ that in the administration of quinine in pernicious malaria it is best rather to sin by prodigality than by parsimony, is open to question. While there are few drugs so potent as quinine having so few toxic

effects, bad results do sometimes follow excessive doses. SCHEL-LONG⁵² noticed that large doses added to the insult to the nervous system and had a depressing effect on the heart. As PLEHN⁴⁰ expresses it, there is a universal tendency to attribute all bad phenomena to the disease and all favorable ones to the remedy. However, after using, in five cases, five to six grams in divided doses, repeated at short intervals during the height of fever, this accurate observer noted considerable depression of the heart, nervous system and general condition of the patients.

Most of the continental writers recommend the Pravaz or Luer syringes with platin-iridium needles, but the ordinary antitoxin syringe, as used by SUTHERLAND¹²² for this purpose, answers as well. A soft rubber tubing connection between the needle and the nipple of the syringe is advantageous, as it may prevent the breaking of a needle in a struggling patient. One of these syringes, a small sterilizing pan and alcohol lamp, do not occupy much space, and being almost indispensable in these cases, should be easily accessible during the malarial season to the physician in a malarial locality, who often sees these cases miles from his office, when time is a matter of life and death. The ordinary hypodermic syringe may be used in an emergency, but to use a sufficient quantity of a properly diluted solution, a number of injections have to be made.

The best location for injection is in the gluteal region well above the ischial tuberosities, though the interscapular region is often chosen.

The technic of intramuscular injections of quinine may be summarized in these precautions: Have the solution freshly made, thorough, dilute and sterile; render the syringe and the injection site aseptic; insert the needle into muscular tissue and avoid breaking the needle.

In 1890 BACELLI¹²³ introduced the intravenous administration of quinine in the treatment of pernicious malaria, claiming thereby to have reduced the mortality from 17% to 6%. The following formula was used:

Quinine hydrochlorate	1 gm.
Sodium chloride	.75 gm.
Distilled water	10 cc.

The arm is bound above the elbow in order to distend the veins of the forearm, into one of which the needle is introduced

in the direction of the blood current, and the solution injected very slowly after removing the constriction. The puncture should be covered with a sterile dressing. The solution should be warm and sterile, and care should be taken that no air is injected. If swelling occurs at the site of injection it is evident that the vein has not been entered. It is said that one gram of quinine thus injected produces a solution in the blood of 1:5000, which is the strength deemed necessary by BINZ to destroy protozoa. ROGERS¹²⁴ thinks well of this method and has abandoned in favor of it the subcutaneous route. However, it probably has no advantages over the intramuscular administration. Moreover, it is not infrequently almost impossible to locate the veins, especially in young negroes.

Quinine dissolved in normal salt solution given by hypodermoclysis has been recommended by GRALL¹²⁵ and others. It is extolled especially by GLATARD¹ in the treatment of children suffering with pernicious malaria. This method is probably not adapted to the treatment of algid malaria on account of the deficient superficial circulation. Besides, the necessary apparatus is frequently wanting.

Just as antisiphilitics may cause the gumma to melt rapidly, but are powerless to restore the tissue it has destroyed, so quinine has its limitations in the therapeutics of malaria. It should be borne in mind that in its relation to the parasites quinine is a toxin, but not an antitoxin. It is possible that where the parasites are accumulated to the extent of thrombosis the quinine in solution in the blood does not reach them in toxic quantities, and where perivascular exudation, hemorrhage and necrosis have resulted from these thrombi, the annihilation of the parasites avails nothing. This is corroborated by those cases ending fatally, notwithstanding a rapid disappearance of the parasites, and in which post-mortem these secondary changes are found. All that can be expected of quinine is to destroy the parasites, and this it may fail to accomplish from not being absorbed, or not being present in the blood in sufficient quantities or at the time when the parasites are most susceptible to its action, or on account of thrombotic occlusions it may not gain access to the parasites causing the symptoms. Quinine is probably a true specific in those cases of pernicious malaria only in which, in the absence of irreparable changes due to toxins or to thrombi,

the prompt destruction of the parasites would be attended by an almost simultaneous cessation of symptoms.

Other than the specific treatment there are important symptomatic indications to be met.

In cases with high temperature and hot, dry skin, cooling baths should be used. For heart depression strychnine or digitalis are useful.

In the cerebral types the ice bag to the head is called for and an active cathartic should be given if possible. Where this cannot be swallowed a drop of croton oil on the back of the tongue may be tried. If delirium is marked a solution of chloral and the bromides should be given by the rectum. Where there are convulsions, chloral and bromides by the rectum, morphine hypodermically, or even inhalations of chloroform may be necessary. BELL³⁵ employed lumbar puncture in a case of malarial coma to relieve the increase in the cerebro-spinal fluid which usually exists in these cases, but the result was disappointing.

In algid attacks for the relief of cold surface and dyspnoea, especially if choleraic symptoms are present, nothing is so suitable as a combination of morphine and atropin. The heart usually requires stimulation by strychnine and digitalis. Hypodermics of ether may be necessary. If dysenteric symptoms arise they should be treated with opium and bismuth, together with saline irrigations.

If complications appear they should receive appropriate treatment.

During convalescence a tonic of strychnine, arsenic, iron and quinine is usually indicated. In cases where it is feasible a change of climate should be ordered until recovery is thoroughly established.

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